LETTER TO THE EDITOR

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Alteration of p62/SQSTM1 Expression Is Uncommon in Gastrointestinal and Prostate Cancer Tissues

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Sequestosome 1 (p62/SQSTM1) contains multiple domains that interact with key components in cellular processes and signaling, including autophagy, nuclear factor-κB (NF-κB) activation, and oxidative stress signaling.[1] p62 behaves as an adaptor between autophagic machinery and ubiquitinated proteins and promotes autophagic degradation of ubiquitinated targets. Altered autophagy is accompanied by p62 accumulation and ubiquitinated proteins.[1] p62 activates NF-κB signaling through binding with TRAF6 and RIP1. Additionally, by interacting with the Nrf2 binding site in Keap1, p62 competitively inhibits the Nrf2-Keap1 interaction, thereby activating the transcription of Nrf2 target genes that induces antioxidant responses.[1] With respect to disease involvement, the p62-encoding gene is frequently mutated in Paget's disease of bone.[1,2] With respect to cancer, p62 is involved in many signaling pathways whose functions are important in cancer development. p62 acts either as a tumor suppressor (via the Wnt pathway) or a pro-oncogenic protein (via the NF-κB and mammalian target of rapamycin pathways).[1,2] p62 is highly expressed in breast, lung, gastric, colon, esophageal, and hepatocellular carcinomas and is associated with poor cancer patient prognosis.[3-6] In contrast, a recent study reported that p62 was downregulated in colon carcinomas.[7] The aim of our study was to confirm whether p62 expression is altered in gastric and colorectal cancers and to address whether it is altered in other cancers.

To determine whether alterations of p62 expression are present in other human cancers, we analyzed the expression of p62 in gastric cancer (GC), colorectal cancer (CRC), and prostate cancers (PCa) by immunohistochemistry using 11 tissue microarray (TMA) blocks. Cases of CRC (n=103) originated from the cecum (n=2), ascending colon (n=19), transverse colon (n=6), descending colon (n=4), sigmoid colon (n=28), and rectum (n=44). Cases of GC (n=100) consisted of 50 diffuse, 36 intestinal, and 14 mixed-type GC by Lauren classification, as well as four early GC and 96 advanced GC cases according to the depth of invasion. The PCa cases (n=107) consisted of one case with a Gleason score of 5, 10 with a score of 6, 47 with a score of 7, 10 with a score of 8, and 39 with a score of 9. For immunohistochemistry, we used the ImmPRESS System (Vector Laboratories, Burlingame, CA, USA) with a rabbit polyclonal antibody against human sequestosome 1 (Thermo Scientific, Rockford, IL, USA; dilution 1/2,000). By visual inspection under a microscope, we graded the immunoreactivity as -, +, or ++. Tumor and normal tissues were interpreted as positive by immunohistochemistry when they scored either + or ++. Other procedures for mutation and immunohistochemistry have been described in our previous reports.[8,9] In the immunohistochemistry analysis, normal gastric mucosal epithelial, colonic mucosal epithelial, and prostate glandular cells exhibited positive p62 immunostaining in all cases (Fig. 1). All of the cases exhibited ++ immunopositivity. In the tumors, immunopositivity for p62 was observed in 97 cases (+, three; ++, 94 cases) of GC, 97 cases (+, two; ++, 95 cases) of CRC, and 100 cases (+, two; ++, 98 cases) of PCa. There was no significant difference in the immunopositivity between normal and GC, CRC, and PCa tumor tissues (Fisher exact test, $p>0.05$). There was no significant difference in the immunopositivity between the GC, CRC, and PCa tissues (Fisher exact test, $p>0.05$). There was no association between p62 expression and clinicopathological parameters, including Gleason score, invasion/metastasis, and TNM stage (chi-square test, $p>0.05$). Because p62 is involved in diverse cancer-related signaling, p62 expression has been studied in many cancers. However, our results demonstrated that p62 was expressed well in both normal and tumor cells of GC and CRC tissues and that there was no difference in the expression with respect to the clinicopathological data. Our data from Korean patients are in agreement with earlier data that

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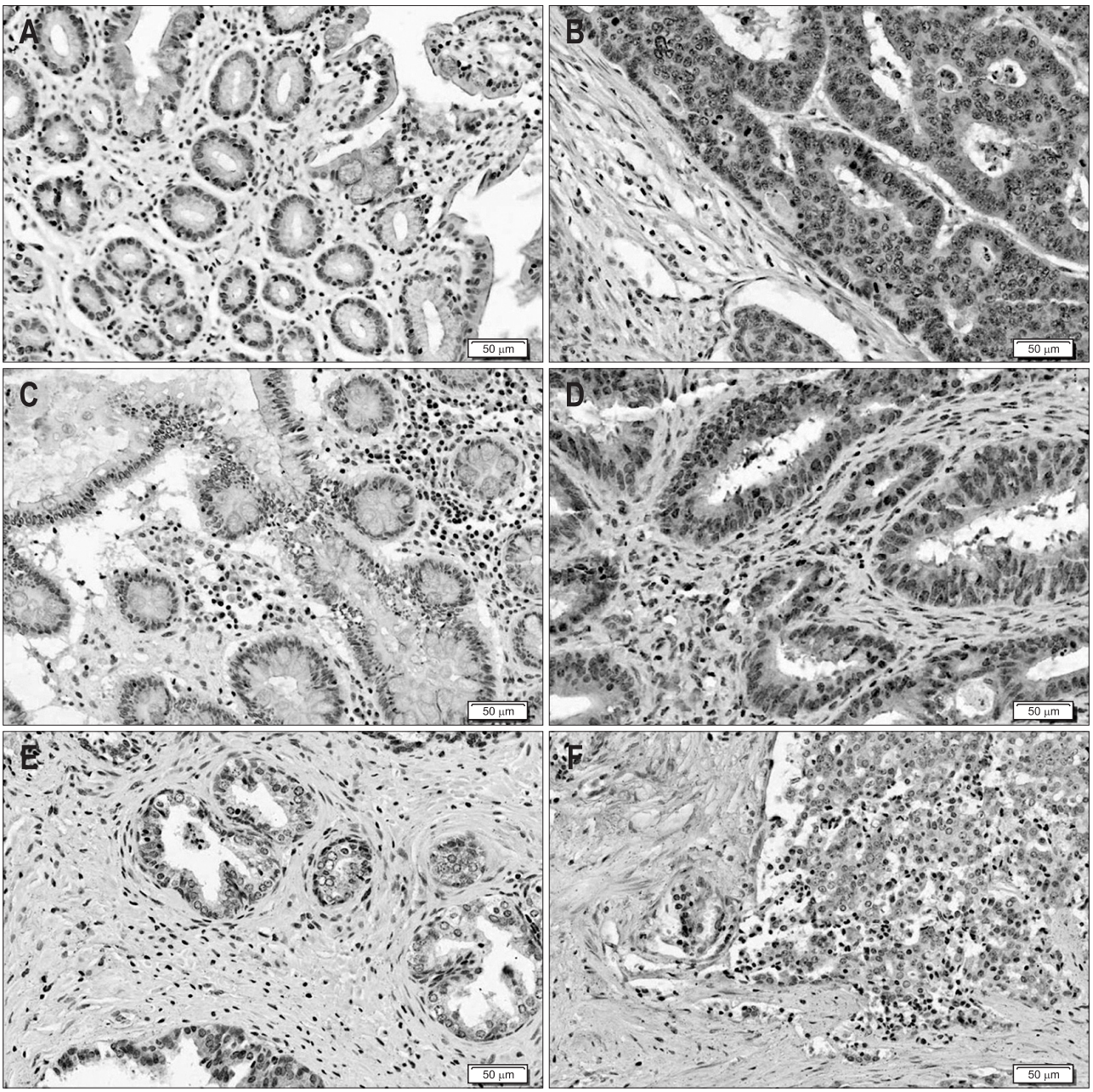

Fig. 1. Visualization of p62 expression in gastric, colorectal, and prostate cancer tissues by immunohistochemistry. (A) Normal gastric epithelial cells exhibit positive immunostaining. (B) In a case of gastric cancer, the cancer cells exhibit p62 immunostaining. (C) Normal colonic epithelial cells are positive for immunostaining. (D) In a case of colon cancer, the cancer cells exhibit p62 immunostaining. (E) Normal prostate glandular cells exhibit positive p62 immunostaining. (F) In a case of prostate cancer, the cancer cells exhibit p62 immunostaining.

demonstrated that both normal and cancer cells in gastric and colon cancers from Chinese patients expressed p62.[6] However, these data are different from other data obtained in a Canadian population that demonstrated decreased expression of p62 in colon cancers compared with the high expression of p62 in normal colonic epithelial cells.[7] One possibility for the disagreement may be ethnic differences (Asian vs Caucasian). Another explanation may be the method we used. Many researchers are concerned about the potential bias in TMAs, mostly due to the heterogeneity of expression patterns in TMA. One way to reduce bias in TMAs is to confirm the data in conventional large tissue sections. To validate the TMA data, we further analyzed the expression in another series of 20 additional colorectal adenocarcinomas and their normal mucosa tissue sections that were more than 1 cm^2 in size and found that p62 was similarly expressed in the tumors (95%) and in the normal mucosa tissues (positive immunostaining in all cases). We also found that p62 expression was not altered in PCa. Our data indicate that alteration of p62 expression is not a common feature in all cancers and that p62 alterations may be tissue-specific.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

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